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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,854	02/22/2002	Jeno Gyuris	GPCI-P02-106	2615
28120	7590	01/28/2004	EXAMINER	
ROPE & GRAY LLP ONE INTERNATIONAL PLACE BOSTON, MA 02110-2624			WESSENDORF, TERESA D	
			ART UNIT	PAPER NUMBER

1639

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/080,854

Applicant(s)

GYURIS ET AL.

Examiner

T. D. Wessendorf

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 November 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-49 and 51-82 is/are pending in the application.
- 4a) Of the above claim(s) 1-47, 53 and 55-80 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 48, 49, 51-52, 53 (in-part), 54, 55 (in-part) and 81-82 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/20/03 has been entered.

Election/Restrictions

Upon a review of the withdrawal of claim 81 from the previous Office action, reconsideration has been made. The claim contains some of the elements of the vector and therefore will be examined with the elected claims.

Status of Claims

Claims 1-49 and 51-82 are pending in the application. Claims 81-82 have been added in the present amendment.

Claim 50 has been canceled.

Claims 1-47, 53 and 55 (in-part), 56-80 (with a random peptide i.e., a library inserted in the vector as shown in the Figures) are withdrawn from consideration.

Claims 48-49 and 51-52, 53 (in-part), 54, 55(in-part) and 81-82 are under examination.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48-49, 51-55 and 81-82, as presently amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In view of the amendments to the claims, the rejection of the previous claims has been obviated. However, the newly amended claims are rejected as follows:

A). Claim 48 is indefinite in the recitation of the prokaryotic cell and eukaryotic cell to describe the vector. These cells are not part of the element that can comprise a vector. Thus, it is confusing as to the use of these cells since these are not elements or a characterizing feature of a vector. It is not clear whether in the eukaryotic cell the test peptide is "expressed" or secreted.

B). Claim 49 is inconsistent with claim 48. Claim 48 does not recite secretion of the test peptide. Rather, expression. It

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is not clear, within the context of the claims, whether these are the same or different.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 48-55 and 81-82 are rejected under 35 U.S.C. 102(e) as being anticipated by Larocca et al (6,054,312) [(as evidenced by either Harper et al (6,232,081) or Mulvihill et al (5,648,254)] for reasons advanced in the last Office action.

Response to Arguments

Applicants contend that Larocca et al disclose that filamentous phage particles displaying a ligand on their surface is used to deliver a therapeutic gene to a cell. Larocca et al specifically teach delivering a fusion protein to a cell. For example, within the context of this invention, the ligand is conjugated to a protein of a bacteriophage, either as

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a fusion protein or through chemical conjugation, and is used to deliver a nucleic acid payload (i.e., therapeutic gene) to a cell (column 10, lines 1-5). Applicants admit that Larocca et al provide a working example showing a vector comprising a chimeric gene comprising FGF2-3 fused to a gene encoding the coat protein III or VIII (see column 37, line 65 to column 38, line 23). But argue that claim 48 as amended, recites a vector comprising a chimeric gene for a chimeric protein, wherein the vector performs differently in a prokaryotic cell as compared to a eukaryotic cell. The claim clearly points out the feature of the vector: in a prokaryotic cell, the chimeric gene is expressed as a fusion protein including the test peptide and the surface protein such that the test peptide can be displayed on the surface of a display packages, whereas in a eukaryotic cell, the test peptide is expressed without the surface protein as a result of the coding sequence for the surface protein being removed by RNA splicing. Applicants submit that Larocca et al. neither disclose nor teach a vector that has these distinct functions in a prokaryotic and a eukaryotic cell. In fact, Larocca et al, as argued, teach expression of a fusion protein between the ligand and a surface protein only.

In response, as admitted by applicants Example 5, col. 37 up to col. 38 Larocca discloses a vector containing a gene

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encoding FGF2-3 genetically fused to either the M13 gene III or gene VIII coat proteins. The copy number of FGF phage coat fusions relative to wild type coat protein is controlled by **displaying** the fusion at high copy number or at low copy number. The FGF-coat protein fusions are tested for phage binding to recombinant FGF receptor by ELISA (i.e., the expression of the displayed FGF2-3 in phage) and also for binding and internalization by immunohistochemistry. The FGF-fusion phage is then further modified by inserting a mammalian reporter gene (e.g., EGFP) expression cassette and SV40 origin of replication (for high copy number replication in cell lines containing T antigen, e.g., COS cells) (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, 1989 for methods and protocols). The modified phage are tested for transduction of EGFP into COS cells by adding the phage to COS cell cultures. The results are quantitated using flow cytometry to measure the distribution of GFP expressing cells in the population and by fluorometry of cell extracts to measure total GFP produced. Thus, this indicates that the secreted GFP is measured and not the GFP fused to phage. Furthermore, Larocca recites at col. 4, lines 11-60, as admitted by applicants, the components of the vector fused to a phage III or VIII and expressed in the prokaryotic cell. Larocca discloses at col. 4,

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line 61 up to col. 5, line 5 that the vector must accept a cassette containing a promoter and a gene. Any promoter that is active in the cells to be transfected can be used. The vector must also have a phage origin of replication and a packaging signal for assembling the vector DNA with the capsid proteins. Other elements may be incorporated into the construct. The construct includes a transcription terminator sequence, including a polyadenylation sequence, **splice donor and acceptor sites**, and an enhancer. Other elements useful for expression and maintenance of the construct in mammalian cells or other eukaryotic cells may also be incorporated (e.g., origin of replication). Because the constructs are conveniently produced in bacterial cells, elements that are necessary or enhance propagation in bacteria are incorporated. Such elements include an origin of replication, selectable marker and the like. The promoter that controls expression of the transgene (i.e., test peptide, as claimed) should be active or activatable in the targeted cell. The present invention will involve transfection of mammalian cells. The choice of the promoter will depend in part upon the targeted cell type and the degree or type of control desired. Examples of promoters include the SV40 early promoter (U.S. Pat. No. 5,118,627), and etc. Furthermore, Larocca discloses at col.9, lines 32-50 the screening of a

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random peptide library fused to the filamentous phage genes VIII. Thus, the teachings of Larocca, taken as a whole, disclose a vector comprising a phage in which a ligand has been fused. The FGF ligand when expressed in a bacterial cell is determined by its binding capability and when secreted in COS cell or mammalian cell is measured by the total FGF-2 produced. There is nothing in the disclosure of Larocca that indicates that the phage has been measured with the total FGF produced. Rather, that the bacteriophage has been used only as a vector (i.e., a carrier) to stably carry or to internalize the FGF to its intended or target site. It is considered that the vector of Larocca would have inherently contained a splice mRNA sites to free the FGF ligand (to enable its measurement) from its carrier (bacteriophage).

Applicants further argue that the teachings of Larocca et al are completely silent on the issue of mRNA splice sites. One of skill in the art has no way of knowing whether the RNA splice sites of Larocca et al flank the coding sequence of the test peptide, or whether they flank other critical DNA elements such as a promoter. The Examiner asserts that Larocca would have inherently known such fact in the art of RNA splicing sites, since Larocca is able to display and secrete the test peptide

indicates that the RNA splices the sites that flank the test peptide to enable its secretion. However, there is no indication that Larocca contemplated a vector that behaves in a eukaryotic cell as presently claimed.

In response, attention is drawn to col. 38, lines 10-17 wherein Larocca discloses the modified vector that is tested for transduction into COS (eukaryotic, as broadly claimed) cells. Furthermore, Larocca is not completely silent as to the issue of mRNA splice sites. Rather, Larocca expressly discloses at col. 5, line 5 said vector as comprising the mRNA splice sites or at col. 30, lines 5-10 incorporating various expression vectors. See particularly U.S. 5,580,967. This mRNA splice sites, is disclosed by Larocca throughout its disclosure. [That the mRNA splicing site is inherent to a cassette expression vector to enable transduction mammalian cells is evident from the teachings of Harper et al at col. 20, line 9 up to col. 21, line 15, which uses the same procedure of Sambrook or Mulvihill et al at col.8, lines 20- 51.) [See also, the instant specification at page 31 which appears to recognize such inherent property of vector with mRNA splice sites. Applicants states that "...A variety of naturally and non-naturally splice sites are available in the art and can be selected for, e.g., optimization in a particular eukaryotic cells selected...."]

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Furthermore, Larocca discloses a specific ligand, FGF. Given this specific ligand one skilled in the art would know where the splice sites exist.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 48-49 and 51-52, 53 (in-part), 54, 55(in-part) and 81-82 are rejected under 35 U.S.C. 103(a) as being obvious over Gyuris et al (US 2002/0025536), alone or in combination with Larocca.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for

the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(1)(1) and § 706.02(1)(2).

Gyuris et al discloses in claim 48 a vector comprising a chimeric gene for a chimeric protein, which chimeric gene comprises (i) a coding sequence for a test antibody, (ii) a coding sequence for a surface protein of a display package, and (iii) RNA splice sites flanking the coding sequence for the surface protein, wherein, in a display mode, the chimeric gene is expressed as a fusion protein including the test antibody and the surface protein such that the test antibody can be displayed on the surface of a population of display packages, whereas in

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the secretion mode, the test antibody is expressed without the surface protein as a result of the coding sequence for the surface protein being removed by RNA splicing. See further claims 49-55. The test antibody is obviously encompassed by the vector containing a test peptide. See Larocca which discloses these different test peptides including antibodies.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 48-49 and 51-52, 53 (in-part), 54, 55(in-part) and 81-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to provide an adequate written description of the components of a test peptide. The specification provides a general statement as to the generic

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test peptide. As stated by applicants in the instant REMARKS, one of skill in the art has no way of knowing whether the RNA splice sites flank the coding sequence of the test peptide, or whether they flank other critical DNA elements such as a promoter. Thus, it is not apparent from the disclosure, as of the filing date, the different test peptides that can be flanked by the mRNA splice sites such that any type of test peptide can be correctly secreted in the eukaryotic cell.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Ill et al discloses vectors and genes exhibiting increased expression.

No claim is allowed.

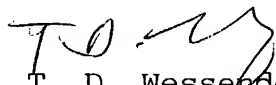
Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (703) 308-3967. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be

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reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-7924 for regular communications and (703) 308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw